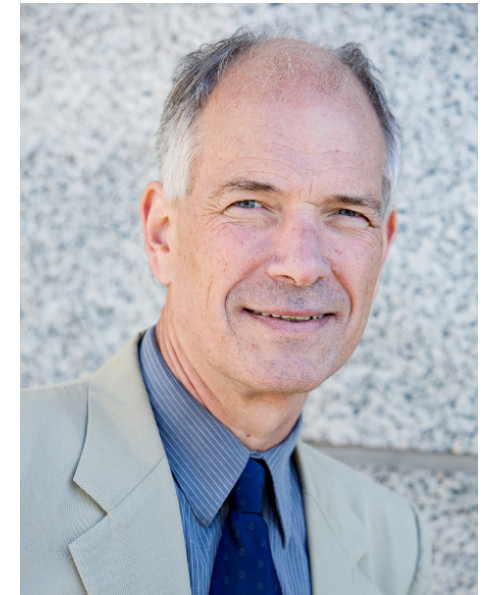


Theme 6: Research Resources, Methods, and Data Infrastructure



Joanne Pike, DrPH

Alzheimer's Association



Vincent Mor, PhD

Brown University School of
Public Health

Identification of People Living with Dementia for Population and Health Care Research



Julie P.W. Bynum, MD MPH

University of Michigan

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Disclosures

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- AHRQ: R01 HS024698
- NICCIH: R01AT009003
- Michigan Dept of Health and Human Services (E20192643-00)

Advisory Roles

- Alzheimer's Association: Consultant
- America's Health Ranking: Advisory board

Identification Strategy of PLWD for Research

Investigator question: How should we identify PLWD for our study?

Response:

What is the purpose of the study?

What inclusion and exclusion features are important for interpretation of results?

What tradeoffs are acceptable in choice of strategy for goals of the study?

✓ **Fitness for Use** of identification strategy needs to be assessed for this research purpose

Diversity of Research Purpose: Today's focus

- **Population/Epidemiology**

- Measure burden of disease
- Assess disparities
- Identify risk factors and inform etiology
- Inform policy development

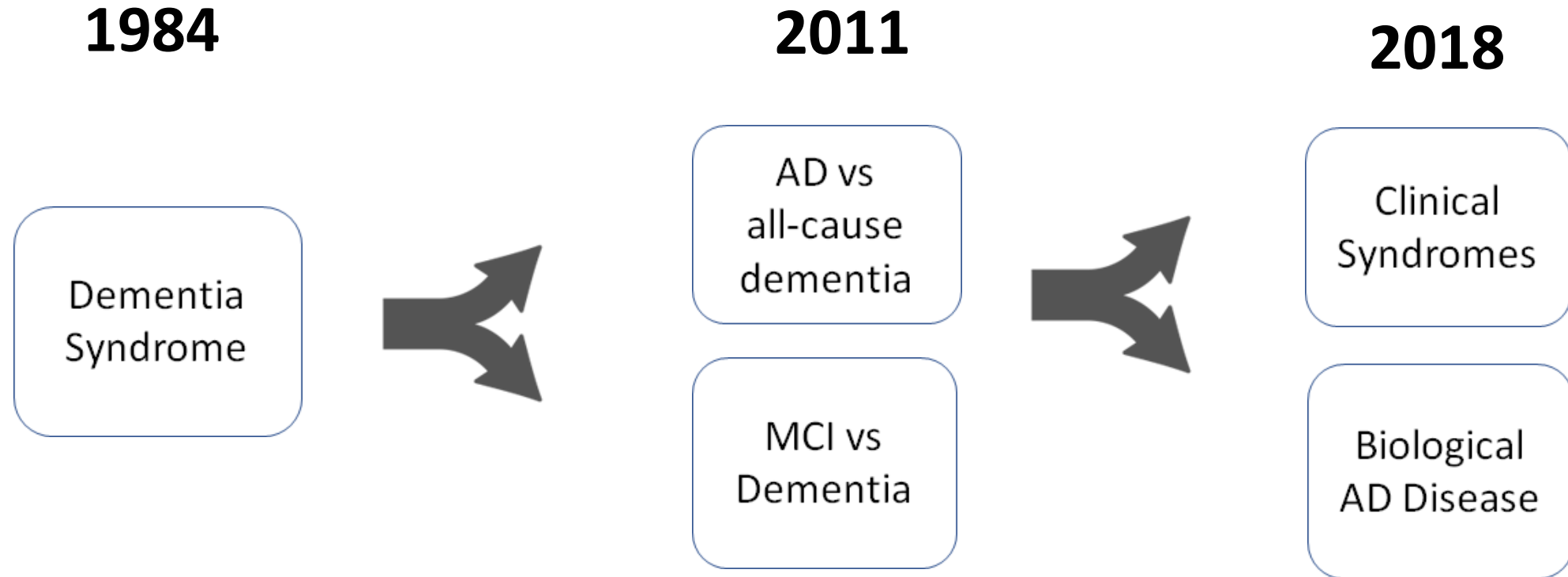
- **Health Care Settings**

- Testing new interventions
- Implementation & dissemination of proven interventions
- Monitor quality of care improvement interventions

✓ Punchline: No one single best approach

Who is a Person Living with Dementia?

Diagnostic Categories for Presence of Clinical Disease



Decline in memory & other cognitive function compared to previous level determined by performance, examination, neuropsychological tests when at a normal level of consciousness.

Epidemiologic Identification Strategies

	Dementia Syndrome	AD vs Other Etiology	MCI vs Dementia	Biological AD Disease
<i>Measurement Requirements</i>				
Objective Cognitive Performance	x	x	x	-
Role or iADL / ADL Function	x	x	x	-
Clinical Evaluation	-	x	+/-	-
Biological Markers	-	-	-	x
<i>Data Collection Considerations</i>				
Diagnostic Precision	Low	Higher	Low	Uncertain
Cost	Low	High	Low/high	highest
Risk to participant (ethics)	Low	Low	Low	higher
Recruitment Barriers (diversity)	Low	Medium	low	high

Challenges for Future Epidemiological Research

- Sampling and recruiting representative populations
 - Cost of conducting studies
 - Variation in measurement across studies
 - Consistency of over time as definitions change
 - Limited biological data for new definitions in particular among racial and ethnically under-represented populations
- ✓ Consider Dementia Disease Construct in Fitness for Use of Strategy
 - ✓ Clearly communicate the construct and impact on interpretation

Healthcare Settings Identification Strategies

✓ Availability of data generated in clinical course of care
Less costly, pragmatic, representative of real world

- Data collected for Billing & Regulatory Purposes

Claims: ex. Medicare, Medicaid, Private Insurers

Assessment files: ex. Nursing home Minimum Dataset

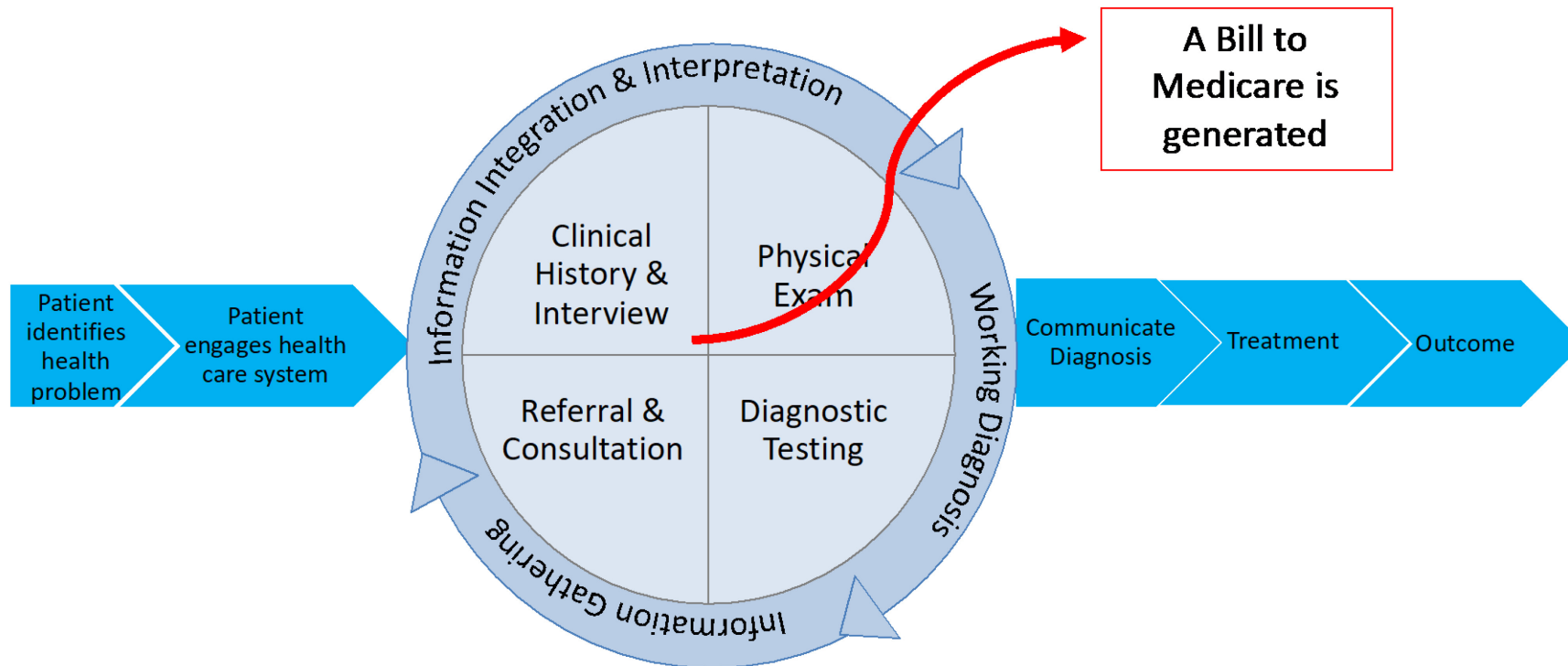
- Electronic Health Record

Structured elements: ex. problem and medication lists

Unstructured elements: ex. clinical text in notes

Challenges of Health Care Data Approach

Conceptual Process of Diagnosis



Diagnosis of Dementia in Health Care Settings

- 62% un-detected in community*
- Potential Reasons for under-diagnosis
 - Stigma
 - Access to care
 - Belief cognitive loss is normal part of aging
 - Clinician skill and comfort with diagnosis
 - Potential negative consequences of disease label
- Accuracy of diagnosis in clinical practice is largely unknown

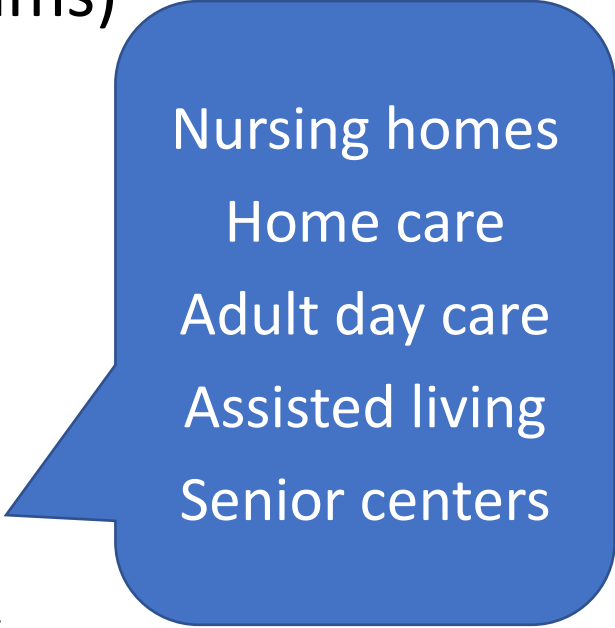
EHR Opportunities and Challenges

Opportunities

- Text fields from clinical notes to extract cognitive symptoms
- Access screening tools uses (ex. annual wellness exams)
- More sophisticated tools that analyze linguistics

Challenges and Gaps

- Still relies on coming into a clinical setting
- Implementation across health systems challenging
- Requires coming into a clinical setting that uses EHR



Nursing homes
Home care
Adult day care
Assisted living
Senior centers

Identification Strategy Beyond Presence of Disease

Stage or Severity

- Cognitive Function
- Role Function
- iADL/ADL Function
- Behavioral Symptoms

Specific Dementia Type

- Alzheimer's Type
- Vascular Dementia
- Frontotemporal Dementia
- Lewy Body Dementia

✓ For Care Interventions:

- When does it matter to delineate the characteristics?
- Are measurement approaches adequate for studies of today?

Summary

- Many new and exciting changes in the field that require greater attention to who and how we identify people living with dementia for research especially over time
- Changes in definitions and availability of new data necessitate careful consideration of how we assure representation of all segments of the population who may benefit
- A call for research use of language and report enough information that accurately reflects to stakeholders what we mean by PLWD and address limits of interpretation dictated by the data sources used

Opportunities for Embedded, Pragmatic Clinical Trials Among People Living with Dementia and their Caregivers



Thomas G Travison, PhD

Harvard Medical School

March 24-25, 2020

Disclosures

- Director, Biostatistics and Data Sciences core
Boston Older Americans Independence Center (P30AG031679)
- Associate Leader, Design and Statistics Core
NIA Imbedded Pragmatic Alzheimer's Disease and AD-Related
Dementias Clinical Trials (**IMPACT**) Collaboratory
(U54AG063546)

Overview of embedded pragmatic trials in PLWD and caregivers

Embedded, pragmatic clinical trials offer promise for developing interventions among people living with dementia (PLWD) and their caregivers

- Purpose: Establish effectiveness of novel non-pharmacologic interventions
- Embedded: Within healthcare delivery systems in the context of routine care
- Pragmatic: mirror clinical practice, use routinely-collected measurements

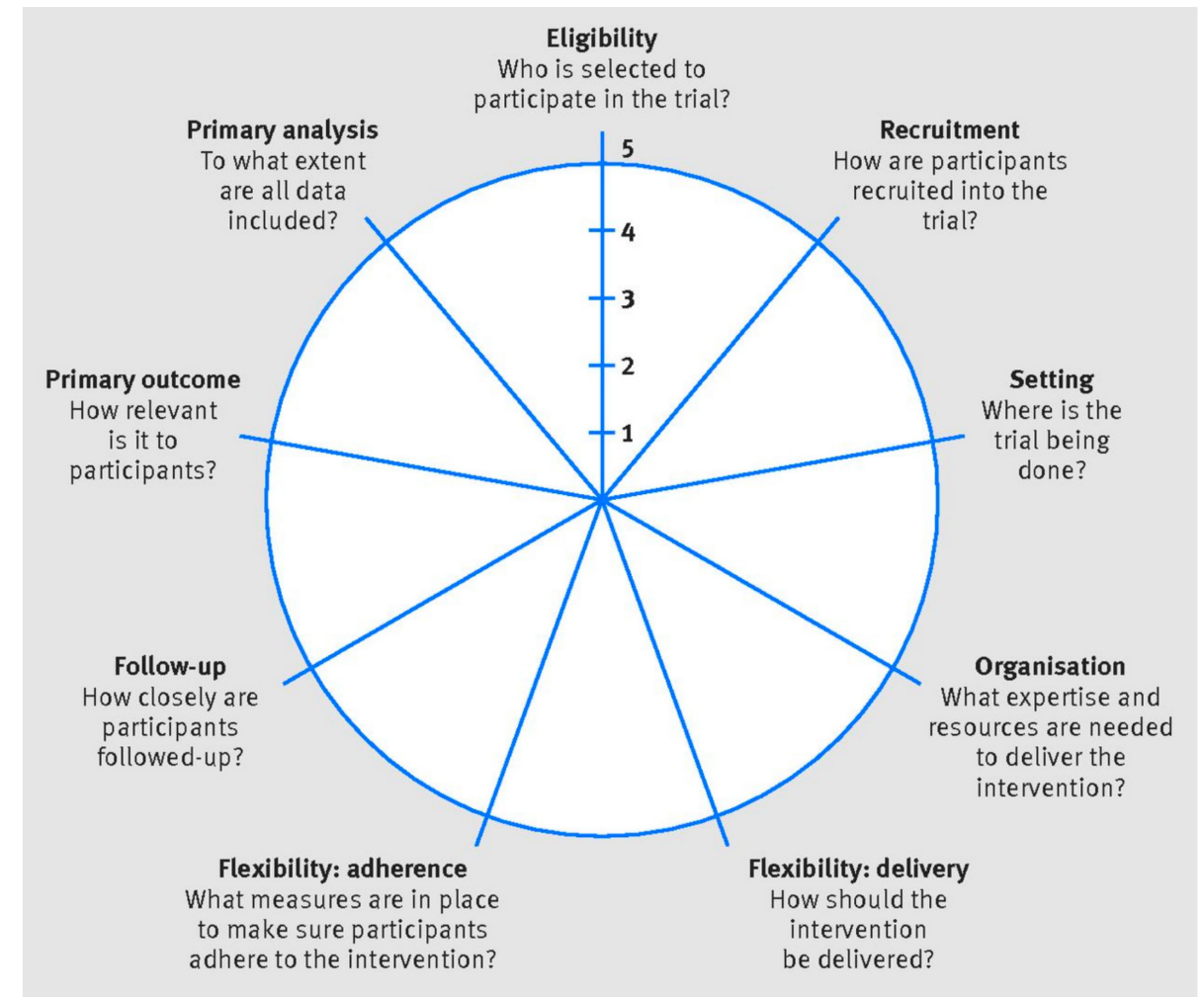
Pragmatic designs enforce relevance to PLWD along several axes

Inclusive

- Few exclusions
- Diversity of settings
- Limited reinforcement of adherence
- Permits assessing / addressing **heterogeneity and health disparities**

Participant – focused

- Flexibility in delivery
- Relevant, meaningful outcomes



Though well-suited to trials among PLWD, pragmatic trials also present considerable challenges

- Design: **where, how, and among whom** will the trial be conducted
- Measurement: **what information** will be obtained, and how
- Interpretation: **what conclusions** will be drawn, **about whom** will they be relevant, and **what caveats** must be acknowledged

Weinfurt et al. *BMC Med Res Methodol* 2017; 17: 144.

Cook et al. *Clin Trials*. 2016;13(5):504-512.

Design features sacrifice some control exerted in conventional randomized trials

- Interventions often require “clustered” randomization (PLWD and caregivers assigned in groups)
 - Allows measurement of systems, facilities, patient-level effects
 - Requires a greater number of PLWD and caregivers to insure valid conclusions
- Diverse populations implies potential variation in effectiveness, fidelity
 - Enhances generalizability
 - May permit estimation of disparities in effectiveness and availability to specific populations

Purely pragmatic **measurement** protocols present additional challenges for trials in PLWD

- Reliance on routinely collected (e.g. EHR) data makes difficult the capture of relevant information
 - Mimics information-gathering and case management in real-world settings
 - May disregard important information, e.g. **patient-important measurements informing perspectives of PLWD and caregivers**
- Connecting results on people living with dementia to their caregivers increases practical complexity
 - Acknowledges connection and feedback within patient/caregiver dyad
 - **Necessitates linking of EHR for participants and caregivers**

Pragmatic trials induce specific considerations in analysis and interpretation

- Identifying mechanism(s) of action and their consistency across subpopulations of patients
- Identifying the influence of the intervention both on PLWD and on caregivers
- Translating higher (e.g. systems)-level conclusions to actions informing patient/caregiver decision making, clinical practice, and policy

Opportunities to enhance impact of
pragmatic research designs for PLWD

Insurance of
readiness of
interventions for
evaluation
increases feasibility
and validity of
findings



Contemporary methodologic innovations address some challenges in design of embedded pragmatic trials

- Contemporary designs that facilitate within-person and within-group comparisons

- e.g. cluster-crossover, stepped wedge

	Period 1	Period 2	Period 3	Period 4	Period 5
Cluster 1		*	*	*	*
Cluster 2		*	*	*	*
Cluster 3			*	*	*
Cluster 4			*	*	*
Cluster 5				*	*
Cluster 6				*	*
Cluster 7					*
Cluster 8					*

- Designs and analyses that explicitly consider the perspectives of PLWD and and caregivers in treatment assignment
 - e.g. patient-preference trials, standardly tailored interventions

Turner et al. *Am J Public Health*. 2017;107(6):907-915.
Monin et al. *Aging Ment Health*. 2013;17(4):508-516.
Hussey et al. *Contemp Clin Trials*. 2007;28(2):182-191.

Hemming et al. *BMJ*. 2015;350:h391
Hooper, Bourke. *BMJ*. 2015;350:h2925.
Kowalski, Mrdjenovich. *Perspect Biol Med*. 2013; 56(1):18-35.
Allore et al. *Clin Trials*. 2005;2(1):13-21

Infrastructural investment and design flexibility may enhance the quality of **measurement**

- Establishing validity and reliability of measures obtained from administrative data and EHR
- **Mixed-methods** incorporating explicit assessment of perspectives of **PLWD and caregivers**
- Techniques for adjudication and use of **surrogate markers of effect**
- **Consider relaxing strict mandates to be 'pragmatic' in assessments** so that outcomes are patient-important and responsive

Lyons, Lee. *J Fam Nurs*. 2018;24(1):8-28.

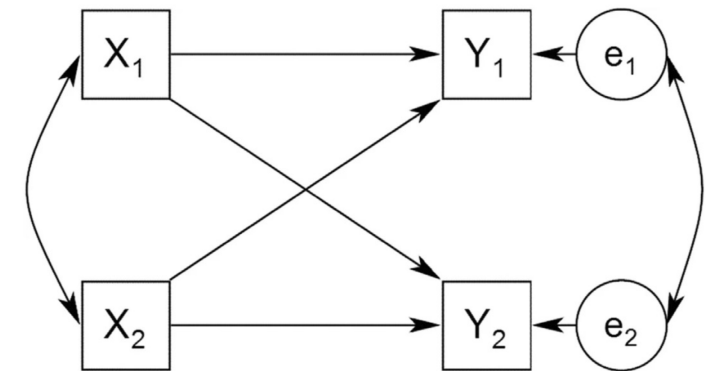
Moniz-Cook et al. *Aging Ment Health*. 2008;12(1):14-29.

A focus on continuous [interdisciplinary engagement](#) promotes success

- Early and continuous engagement of healthcare delivery system
- Early and continuous engagement with clinical practitioners
- Preconceived, multidisciplinary response plan for unanticipated difficulties

Innovations in contemporary methodology creates ease of **interpretation and reproducibility**

- Estimation of effects for specific subpopulations and phenotypes
- Models explicitly addressing and quantifying treatment heterogeneity
 - e.g. Consideration of influence of PLWD / caregiver choices in patient-preference trials
- Models explicitly considering outcomes for PLWD / caregiver **dyads**
- Visualization to demonstrate implications of conclusions on individual patient decisions and outcomes



Maroufizadeh et al. *BMC Med Res Methodol* 18, 117 (2018).

Summary

- Embedded pragmatic trials offer promise in testing novel interventions to improve the health and well-being of PLWD and their caregivers
- Certain design features (flexibility in enrollment, setting, adherence) are immediately applicable in this setting
- Other pragmatic features may need to be relaxed to improve relevance (augmented data capture, use of mixed methods)
- Contemporary design and analysis (crossover trials, tailored interventions, dyadic analysis) may help to bolster impact

References

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- Loudon et al. *BMJ*2015;350:h2147Lyons, Lee. *J Fam Nurs*. 2018;24(1):8-28.
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Consent for Research Involving Dementia: Ethical Considerations



David Wendler, PhD

Department of Bioethics, NIH Clinical Center

March 24-25, 2020

Disclosures

- I have no financial conflicts of interest to disclose.
- I am not a lawyer and will not discuss laws that might be relevant to the present topic.
- The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS or Federal government.

Informed Consent for Research

- Obtaining appropriate informed consent is critical to ethical clinical research.
- However, obtaining consent for dementia research raises a number of important challenges.
- The present talk focuses on two of these challenges.

Question #1: Should participants' decisional capacity be assessed?

Existing Guidance

- Commentators and guidelines tend to focus on evaluating individuals who are *at risk* for lacking decisional capacity.
- For example, the U.S. NBAC recommends formal assessment of potential subjects who suffer from “mental disorders that may affect their decision-making capacity.”
- Members of at risk groups receive formal assessment; others are presumed capable, and receive little, if any, assessment.

Concerns

- Ethical research requires that individuals provide valid consent, not simply that they have the capacity to do so.
- In addition, targeting at risk groups raises the challenge of determining what counts as sufficiently at risk, has the potential to stigmatize targeted groups, and may not offer enough protection for other individuals.

Answer #1: Yes, Assess Everyone

- Assess all subjects' consent, at enrollment and periodically thereafter.

Wendler. *Arch Intern Med* 2004; 164:2201–2204

- Assessing consent requires a functional assessment of whether the individual can consent to the study in question.
- Diagnoses and standardized tests of cognitive capacity (e.g. Mini Mental State Examination) do not determine whether an individual can consent.

Kim, Caine. *Clinical Trial Psychiatr Serv* 2002; 53:1322-1324

Kim et al. *BJP* 2007; 191:38-43

Study Specific Approach

- Minimal assessment is sufficient for low risk studies (e.g. Why do you want to enroll in this study).
- More formal assessment as the risk-benefit profile of the study becomes less favorable to participants.

Instruments

- Several instruments have been developed to assess capacity.

Dunn et al: Am J Psych 2005; 163:1323–1334

- One of the most widely used is the MacArthur Competence Assessment Tool – Treatment (MacCAT-CR).

Appelbaum, Grisso. MacCAT-CR. 2001. Professional Resource Press

Maximize Chances for Success

- Comprehension and consent can be influenced by a range of factors, including quality of the explanation, time of day, level of anxiety, comfort with the setting.
- Prospectively consider steps to increase chances for success.
- If individual “fails” at first, consider whether it may be due to circumstances that can be changed.

Question #2: Who should make research decisions for incapacitated patients (enrollment, continued participation, undergo specific procedures)?

Protect by Excluding

- Some commentators argue individuals who are unable to consent should not be enrolled in research.
- The first principle of the Nuremberg Code states that consent is “absolutely essential” to ethical research.

Nuremberg Code

- This approach protects against research abuses.

Problems with Exclusion

- Blanket exclusion blocks valuable research and excludes individuals from studies that may benefit them.
- Possible to institute safeguards to protect adults who cannot consent while still allowing valuable research on conditions that affect them?

The Ethical Concern

- Decisional incapacity raises concern that investigators might enroll individuals in research that conflicts with their preferences and values.
- Safeguards should protect individuals from “unwanted” research involvement.
- What do the data suggest?

Individuals' Views

- Many individuals are willing to participate in research if they lose decisional capacity, and they support surrogate consent.

Wendler et al. *Am J Psych* 2002; 159:585-591

Muthappanian et al. *Am J Psych* 2005; 162:2389-2391

Karlawish et al. *Am J Psychiatry*. 2009; 166:182–188

Kim et al. *Neurology* 2009; 72:149–155

De Vries et al. *Am J Geriatr Psychiatry* 2013; 21: 364-372

- Willingness decreases as the risk/benefit profile becomes less favorable; some do not want to participate if they become incapacitated.

Answer #2: Appropriate Surrogates

- Enrollment decisions should be based on the *specific* individual's preferences and values.
- To implement this protection, decisions regarding enrollment and continued participation should be made by an appropriate surrogate using substituted judgement:

Which decision is consistent with the individual's preferences and values?

Appointed Research Surrogates

- A few individuals appoint a surrogate for research prior to becoming impaired.
- In addition, many individuals who cannot consent are able to appoint a surrogate for research: 37.7% of those incapable of consenting to a drug RCT and 54.4% of those incapable of consenting to a neurosurgical RCT were capable of appointing a surrogate.

Kim et al. Arch Gen Psychiatry 2011; 68:214-220

Substituted Judgement

- Encourage individuals to document/discuss their preferences and values regarding treatment and research participation early in the course of the illness (e.g. NIH Advance Directive).
- Require greater evidence that participation is consistent with the individuals' preferences and values as the risk-benefit ratio of the research becomes less favorable for them.

Outstanding Questions

Supported Decision Making?

- Capacity assessments typically assume patients need to be able to make decisions *for themselves*.
- To what extent can we assist patients with dementia to make research decisions?

Kohn et al. Penn State Law Review 2013; 117:1111-1157

Seamless Approach?

- Should individuals be informed they are not capacitated?
- Or: identify surrogates early and engage both the person living with dementia and the surrogate in decision making without ever identifying the point of decisional incapacity?

Dukoff, Sunderland. *Am J Psychiatry* 1997; 154:1070–1075

Who Can be a Surrogate?

- Must individuals who serve as research surrogates be appointed by the individual or are next of kin surrogates appropriate?
- If they must be appointed, must they be appointed for research, or are individuals appointed to make clinical care decisions appropriate for research?

Surrogate Assessment?

- There has been a good deal of attention on assessing patients' decisional capacity.
- There has been less discussion of assessing surrogates' decisional capacity.
- Should surrogates be assessed to ensure they are appropriate?

What Counts as Dissent?

- What counts as dissent sufficient to stop research: “I want to go home”; “I am really tired”, “I feel like I have had enough”
- Non-verbal individual pulls arm away from a needle stick?

Summary

1. Should participants' decisional capacity be assessed: Yes
2. Who can make research decisions for incapacitated patients: Appropriate surrogate using substituted judgement
3. Important questions remain!

References

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Saks et al. *Yale J Health Law Policy Ethics* 2008; 8:37–78

Kim. *Nat Rev Neurol* 2011; 7:410–414

Abdoler, Wendler. *JERHRE* 2012; 2:37–50

Theme 6: Gaps and Opportunities 1

Develop a public-private consortium in the form of a National Center for Excellence in care to serve as a repository for secure data access techniques, research and analytic models, and implementation and dissemination strategies promoting interventions that can improve the lives of persons living with dementia and their care partners.

Theme 6: Gaps and Opportunities 2

Undertake research to test the value of machine learning and artificial intelligence approaches designed to identify persons living with dementia and their care partners in EMR and health insurance claims, and to readily measure their needs for services and outcomes of care.

Theme 6: Gaps and Opportunities 3

Conduct research on methods to engage payer and provider organizations in applied research on dementia-related care, services, and supports.

Theme 6: Gaps and Opportunities 4

Develop measures and approaches to monitor the adoption and dissemination of dementia capable communities.

Theme 6: Gaps and Opportunities 5

Evaluate new and modified measures for identifying and characterizing people living with dementia who may benefit from dementia care interventions being tested in population-based and healthcare system-based studies and for monitoring progress toward identified milestones at the national, state, and community-levels.

Theme 6: Gaps and Opportunities 6

Promote research that integrates different techniques to identify cognitive impairment including imaging, bio-markers, cognitive testing and functional assessment in order to estimate the relative contribution of each approach to disease staging systems necessary for research.

Theme 6: Gaps and Opportunities 7

Develop infrastructure (measures, surveys, reporting systems) for population-based studies of persons living with dementia and care partners to monitor progress toward meeting national, state, and community milestones, including key subpopulations of interest.

Theme 6: Gaps and Opportunities 8

Promote the translation of effective dementia programs and services to real-world settings by conducting innovative research using designs that increase the generalizability of research findings including pragmatic trials; quasi-experimental designs; hybrid designs; mixed methods; rapid-cycle quality improvement methods; and standardized process measurement and consider incorporating community-based participatory research and practice-based research models to facilitate this translation.

Theme 6: Gaps and Opportunities 9

Develop and test new approaches to engaging persons with cognitive impairments in research who may not have the capacity to provide consent using traditional standards. Conduct research on the use of assent and dissent, with special consideration for understanding capacity, beneficence, and access to research both for individuals with dementia and their care partners.

Theme 6: Gaps and Opportunities 10

Conduct research to guide Institutional Review Boards and ethics committees on how to facilitate the appropriate collection of self-report data from persons living with dementia and their caregivers.

Panelists



Joe Chung, MS

Kinto



Craig W. Thomas, PhD, MS

Division of Population Health,
Centers for Disease Control and
Prevention



Maggi C. Miller, MS, PhD

Arnold School of Public Health,
University of South Carolina

Q & A